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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
|---|---|---|---|
| 09/082,247 | 05/20/98 | NADEAU J | P-2221R1 |

HM12/0622

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| EXAMINER | |
|---|---|
| HOUTTEMAN,S | |
| ART UNIT | PAPER NUMBER |
| 1655 | 2 |

DATE MAILED: 06/22/99

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

# Office Action Summary

| Application No. | Applicant(s) |
|---|---|
| 09/082,247 | Nadeau et al. |
| **Examiner** | **Group Art Unit** |
| Scott Houtteman | 1655 |

☒ Responsive to communication(s) filed on *12/31/98 and 2/08/99*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claims**

☒ Claim(s) *1-50* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-50* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

**Application Papers**

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *1, 2*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

☒ CERT. UNDER 37 CFR §3.73(b)

*--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---*

FORMAL MATTERS

1. Applicant's offer to surrender the original patent grant is acknowledged. Applicant is reminded that the original patent, or an affidavit or declaration as to loss or inaccessibility of the original patent, must be received before this reissue application can be allowed. See 37 CFR 1.178. This requirement can be held in abeyance until allowance is indicated.

2. The reissue declaration filed with this application is defective because it fails to contain a statement that all errors which are being corrected in the reissue application up to the time of filing of the oath/declaration arose without any deceptive intention on the part of the applicant. See 37 CFR 1.175 and MPEP § 1414.

The declaration contains words very close to this in meaning, for example on page 1 and page 5: "inadvertent error without any deceptive intent" and "These errors arose without any deceptive intent . . ." However, the declaration does not contain a statement with the exact same meaning as 37 CFR 1.175: *All errors* which are being corrected in the reissue application *up to the time of filing of the oath/declaration arose* without any deceptive intention on the part of the applicant. (emphasis added) This rejection can be overcome simply by adding the statement to the declaration:

> "All errors which are being corrected in the reissue application up to the time of filing of the oath/declaration arose without any deceptive intention on the part of the applicant."

See MPEP 1414, Section III.

3. Claims 1-50 are rejected as being based upon a defective reissue declaration under 35

U.S.C. 251 as set forth above. See 37 CFR 1.175.

The nature of the defect(s) in the declaration is set forth in the discussion above in this Office action.

4. Assignees have not established ownership interest in the patent by strictly complying with the provisions of 37 CFR § 3.73(b). See MPEP §§ 1410.01, 324.

While the file contains some effort to establish ownership interest, this effort is missing some elements. For example, applicants have filed a "PETITION AND OFFER TO SURRENDER ORIGINAL PATENT GRANT" which mentions an order for a title report. The file also contains a paper specifying where the title is recorded in the Office. These documents, however, are not signed by a party authorized to act on behalf of the assignee or a person averring to be empowered or authorized to sign on behalf of the assignee. This rejection can be overcome by filling out the attached "CERTIFICATE UNDER 37 C.F.R. § 3.73(B)." (A copy of this form can also be found in the MPEP § 324.)

5. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

NEW MATTER REJECTION

6. Claims 21-42 are rejected under 35 U.S.C. 112, first paragraph. They contain subject

matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 21-42 are drawn to coupling a "secondary amplification" to the Polymerase Chain Reaction (PCR) amplification method.

The originally filed specification, however, does not describe PCR coupled to the "secondary amplification." Instead, the specification describes Strand Displacement Amplification (SDA) coupled to the "secondary amplification." SDA is a materially different amplification method and the skilled artisan would not reasonably conclude that one had possession of the PCR coupled amplification given the specifications description of the SDA coupling.

SDA is distinct from PCR. SDA requires a nick be made near the 5' end of the target nucleic acid. In PCR there is no nick. PCR Amplification proceeds by extension of a primer which is annealed to the 5' end of a template. Another distinction is that SDA amplification proceeds without a specific strand separation step. In SDA, the newly synthesized strand growing from the nick "displaces" the nascent strand. In PCR the "nascent" strand is removed by a specific strand separation step, typically a heat denaturation step.

In describing the secondary amplification invention, the specification consistently refers SDA as the coupled amplification process. There is no mention of PCR coupled to the secondary amplification anywhere in the specification. Furthermore, when PCR is mentioned, it is to contrast that reaction with the coupled SDA/secondary amplification reaction. See for example col. 2 first full paragraph.

Also, the specification suggests that coupling the secondary amplification to PCR would lead to undesirable results of "high levels of background signal." The specification discloses . . . "high levels of background signal" when the [signal] primers are capable of functioning as amplification primers (Specification col. 6, lines 33-36)." The specification discloses as follows. (Note that the signal primers mediate the secondary amplification):

> "It is an important feature of the invention that the signal primers do not function as amplification primers in the SDA reaction in which they are employed. [Specification, col. 6, lines 25-28.] . . . As the secondary amplification product does not contain nickable restriction endonuclease recognition sites, it is not amplifiable in the SDA reaction and remains effectively inert throughout the remainder of the amplification reaction, but additional copies of the secondary amplification product are generated from the target sequence. [Specification col. 7, lines 44-50]

Since the primers used with PCR are the same as those used in the secondary amplification (both function without being nicked), the signal primers *would* function as amplification primers and thus lead to "high levels of background signal."

Therefore, in view of the material differences between PCR and SDA, the lack of any description of PCR coupled with secondary amplification and the use of PCR to contrast with the SDA/secondary amplification reaction, the skilled artisan could not have reasonably concluded that the inventors had possession of PCR coupled to the amplification reaction.

ENABLEMENT REJECTION

7. Claims 21-42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the

art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 21-42 broadly recite (1) a nucleic acid amplification reaction (which reads on PCR amplification; (2) a secondary amplification and (3) signal primers which may function as amplification primers in the PCR amplification. The specification, however, explicitly warns that "an important feature" is that "the signal primers do not function as amplification primers." As currently drafted the claimed method would lead to "high levels of background signal" as evidenced by explicit warnings in the Specification, as explained above in the NEW MATTER rejection.

The claimed signal primers will work in the PCR amplification reaction because the signal primers have all of the essential characteristics of amplification primers. They hybridize to the target and can be extended to produce a "signal primer extension product." Given this characteristic, the signal primer will also participate in the claimed "nucleic acid amplification reaction" comprising the "first amplification primer" and thus result in a high background signal.

There is no guidance or examples in the specification explaining how to use signal primers which will participate in the amplification reaction while avoiding the "high levels of background signal." The specification merely warns against using signal primers unless one is performing an SDA amplification reaction in which the signal primers will not participate.

In view of the breadth of the claims, lack of guidance, and lack of examples, it would have required undue experimentation of a skilled artisan to overcome the high background signal problems and therefore the invention not enabled

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 43-50 are rejected under 35 U.S.C. 102(b) as being anticipated by Mullis et al. US Pat. 4,683,195; 7/1987 (Mullis) or Urdea, US Pat. 5,200,314; 4/1993.

Claims 43-50 are drawn to signal primers and amplification products comprising: target binding sequence, extendible 3' ends, and labels such as haptens, antibodies and other affinity ligands; radio isotopes, dyes and enzymes and primers having a "special nucleotide sequence" such as a restriction endonuclease recognition site and a signal primer hybridized to an amplification product.

Mullis teaches primers with target binding sequences which are labeled with radio isotopes and the primer/amplification product hybrid. See Mullis et al. col. 21, lines 30-32, col. 22, lines 3-5 and col. 8, lines 9-19 and col. 10, lines 25-46 (hybridization of primers to amplification product).

Urdea also teaches primers with target binding sequences which are labeled with radio isotopes and the primer/amplification product hybrid. Labels such as radiolabels ($^{32}P$) photochemical, fluorescent dyes, enzymes, biotin, haptens, antibodies etc are specified. See Urdea for example, col. 9, lines 20-27; col. 5, lines 21-34 and col. 17, lines 16-20.

A protest was filed on 12/31/98 by Ms. Teskin and a response was filed on 2/08/99 by Mr. Highet.

The protest raises the following issues

(1) The enablement and descriptive support of claims 26 and 36, detection of restriction endonuclease cleavage product absent separation of the products. See protest pages 4-18.

(2) The anticipation of the signal primers. See protest pages 18-21.

(3) Protesters conclusion that the scope of the newly presented claims, reciting amplification, is essentially the same as that of the original claims reciting SDA. See protest page 21

(4) At various points, protester alleges assignee has violated the duty of disclosure under 37 C.F.R. § 1.56, and alleges an intention to use "a smoke screen to disguise the real intent of the present reissue." See for example protest pages 17 and 21.

The response deals soles with the protestors allegations of lack of good faith and violations of the duty of disclosure.

(1) With respect to the Protestors suggested enablement and descriptive support rejections, the examiner finds the protestor's arguments unpersuasive and this rejection was not raised.

The claims are not too broad with respect to the issue of detection without a size separation step. It is not sufficient to allege that a claim reads on an inoperable embodiment because a claim can read on inoperable embodiments but still be of the right scope so long as the skilled artisan has sufficient guidance as to which embodiments are enabled and which are not.

Accordingly, the protestor must also show that there is a lack of guidance as to which embodiments are enabled and which are not. This showing is missing in the present case.

Protestor is interested in a particular embodiment which protestor alleges is within the scope of claims 26 and 36, and is not enabled. This embodiment is disclosed in Protestor's patent 5,763,181, a detection of restriction endonuclease cleavage products using fluorescence which can be done without separation. Protestor argues that "Enablement of such technology was not . . . straightforward," and that "reaction conditions," what linkers may be used to attach the fluorophores to the oligonucleotide primers, and how distance between the fluorophore and the DNA, or between separate fluorophores, can be a significant consideration is designing a detection assay and "in designing [one embodiment] the inventors had to carefully consider how far apart, on the oligonucleotide, to attach the donor and acceptor fluorophores. . . ." etc. Taking all of these facts as true, for the sake of argument, the examiner concludes that the skilled artisan could readily see that these embodiments are not enabled by the current specification and thus there is no lack of guidance.

To hold otherwise would lead to absurd results. For example, these claims are generic with respect to other aspects of the invention, for example, the type of polymerase used. The claims, therefore, read on the use of any polymerase. Using the logic of the protest, the claims would have to be limited only to known polymerases because the specification does not enable the development of new polymerases which would require complex protein engineering. Clearly, however, the claims only encompases the use of prior art polymerases as they are used in standard prior art methods. For this reason, claims can be drafted so that only the critical features are

addressed with specific limitations. The rest of the claimed subject matter is recited in short generic clauses or, if possible, left out of the claim entirely.

An equally troubling result is that the protestor has not argued the enablement of broader claims, for example the base claim for claim 26, claim 21. Thus, according to protestor, a broad claim can be fully enabled while a narrower version of that claim is non-enabled.

Finally, it is important to note that the issue of whether applicant's claims actually do read on protestors invention (an thus whether protestor needs to license the invention from the applicant) need not be resolved here. This issue can be left to be resolved in another forum. It is not necessary to the question of enablement which is the sole issue to be resolved here. For the reasons above, the claims are enabled whether or not applicants claims read on the protestors invention.

With respect to protestors new matter rejection, since the scope of the claims at issue are merely the scope of the prior art detection methods, support is inherent in the specification and thus claims 26 and 36 are adequately described with respect to the detection methods.

(2) With respect to the Protestors suggested anticipation rejection, the protestors arguments are addressed within the text of the examiner's anticipation rejection.

(3) With respect to the Protestors scope argument. These arguments are not persuasive. The newly presented claims have a substantially different scope as explained in the rejection under 35 U.S.C. § 112, first paragraph, description.

(4) With respect to the duty of disclosure and bad faith issue in the protest and in the response. The examiner makes no comment as directed by 37 C.F.R. § 1.291(b), MPEP 1901.

(Allegations of "fraud,' 'inequitable conduct,' or failure of one's 'duty of disclosure' are placed in the file without comment.)

10. Claims 1-20 are allowable over the prior art. The closest prior art, Holland et al. Clinical Cheistry 38(3):462-63, (1992), teach the production of a secondary product from a PCR amplification, an amplification specific exonuclease digestion of a labeled probe. Holland et al., however, neither teach nor suggest a secondary PCR amplification reaction which is linked to, but does not interfere with, the primary SDA reaction.

11. Papers relating to this application may be submitted to Technology Center 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Technology Center 1600 Fax numbers are (703) 305-3014 and 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott Houtteman whose telephone number is (703) 308-3885. The examiner can normally be reached on Tuesday-Friday from 8:30 AM - 5:00 PM. The examiner can also be reached on alternate Mondays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached at (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center receptionist whose telephone number is (703) 308-0196.

Scott Houtteman
June 19, 1999

SCOTT W. HOUTTEMAN
PRIMARY EXAMINER